

## CLAIMS

1. Process for the in situ preparation of chiral compounds derived from oxazaborolidine-borane complexes, characterized in that it comprises the following steps:

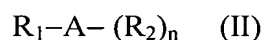
1) the following are added to a suspension of a metal borohydride defined by formula (I):



in which:

M is in particular a sodium, potassium, lithium or zinc ion and preferably a sodium ion:

a) a Lewis base of general formula (II) below:



in which:

R<sub>1</sub> and R<sub>2</sub>, which are identical or different, are an optionally substituted, linear or branched alkyl, an optionally substituted aryl, an alkylaryl or a C<sub>4</sub>-C<sub>7</sub> cycloalkyl, or

R<sub>1</sub> and R<sub>2</sub> together form a C<sub>1</sub>-C<sub>7</sub> alkyl chain or an optionally substituted C<sub>1</sub>-C<sub>7</sub> carbocycle;

n is equal to 1 or 2; and

A is a nitrogen, oxygen, sulfur or phosphorus atom; and

b) an inorganic acid ester of general formula (III) below:



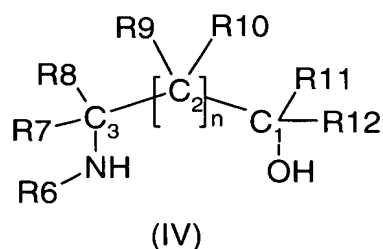
in which:

X is a sulfonyloxy ester group (−OS(O)<sub>2</sub>OR<sub>4</sub>), a sulfonate (−OS(O)R<sub>5</sub>) or a sulfite (−OS(O)OR<sub>5</sub>); and

R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>, which are identical or different, are a linear or branched alkyl optionally substituted by a halogen atom, an aryl, a heterocycle, a heteroaryl, an alkoxy group, an alkylthio group, an alkylaryl group or a C<sub>4</sub>-C<sub>7</sub> cycloalkyl, or

R<sub>4</sub> and R<sub>5</sub> together are a C<sub>1</sub>-C<sub>7</sub> alkyl chain or an optionally substituted C<sub>1</sub>-C<sub>7</sub> carbocycle;

2) and then, to the product obtained after step 1, is added an optically active amino alcohol of general formula (IV) below:



in which:

R<sub>6</sub> is a hydrogen atom, a linear or branched C<sub>1-8</sub> lower alkyl group, preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or pentyl, or a C<sub>1-15</sub> arylalkyl group, preferably benzyl, phenylethyl or methylbenzyl, which can optionally be substituted by a C<sub>1-5</sub> alkoxy or alkyl of the methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, methoxy, ethoxy, propoxy, butoxy or pentoxy type;

R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub> and R<sub>12</sub>, which are identical or different, independently are a hydrogen atom, organic radicals such as a C<sub>1-8</sub> lower alkyl group, especially of the methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or pentyl type, a C<sub>6-12</sub> aryl group, especially of the phenyl, 1-naphthyl or 2-naphthyl type, or a C<sub>7-12</sub> arylalkyl group, especially of the benzyl, phenylethyl or methylbenzyl type, it being possible for said aryl or arylalkyl groups to be substituted by a C<sub>1-5</sub> alkyl or a ... such as mentioned above, with the proviso that R<sub>6</sub> and R<sub>7</sub> are different;

R<sub>6</sub> and R<sub>7</sub>, or R<sub>7</sub> and R<sub>11</sub>, or R<sub>8</sub> and R<sub>9</sub>, or R<sub>10</sub> and R<sub>11</sub> together can form an optionally substituted C<sub>3-6</sub> lower alkylene group, preferably a methylene, dimethylene, trimethylene or tetramethylene group;

R<sub>8</sub> and R<sub>9</sub> together can form an alkylene group that is optionally substituted

or fused with a benzene ring, preferably trimethylene, tetramethylene, penta-  
methylene, o-phenylenemethylene or o-phenylenedimethylene;

n is equal to 0, 1, 2 or 3; and

C<sub>1</sub> and/or C<sub>2</sub> and/or C<sub>3</sub> are an asymmetric carbon atom.

5

2. Process according to claim 1, characterized in that said compound of  
formula (II) is a linear or cyclic ether, preferably tetrahydrofuran or tetra-  
hydropyran; a secondary or tertiary amine, preferably N,N-dimethylamine, N,N-  
diethylamine, aniline, N,N-diethylaniline or N-ethyl-N-isopropylaniline; a linear or  
10 cyclic thioether, preferably dimethyl sulfide; an amino ether, preferably  
morpholine; or a phosphine, preferably triphenylphosphine, the compound of  
formula (II) particularly preferably being N,N-diethylaniline (DEA).

3. Process according to claim 1 or 2, characterized in that said compound of  
15 general formula (III) is a dialkyl sulfate, a sulfuric acid bisaryloxyalkyl ester, a  
bisalkoxysulfonyloxyalkane, a dioxathiolane dioxide and particularly preferably  
dimethyl sulfate (Me<sub>2</sub>SO<sub>4</sub>).

4. Process according to any one of the preceding claims, characterized in that  
20 the amounts of Lewis base and inorganic ester are between 1 and 2 equivalents,  
based on the metal borohydride.

5. Process according to any one of the preceding claims, characterized in that  
the compounds (I), (II) and (III) are brought into contact in step 1) in any order at a  
25 temperature of between 0°C and 75°C and the resulting reaction medium is stirred  
at room temperature for a period of between 0.5 and 4 hours.

6. Process according to any one of claims 1 to 5, characterized in that in step  
2) the following are added to the product obtained after step 1):  
30 a halide defined by formula (X):



in which:

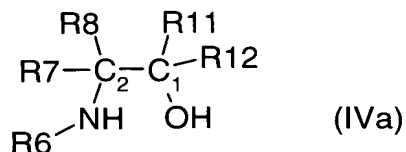
35 M<sub>1</sub> is selected from a sodium, potassium or lithium ion, an ammonium

group and a phosphonium group; and

Y is a halogen atom such as chlorine, bromine, fluorine or iodine;

and then the optically active amino alcohol of formula (IV).

- 5 7. Process according to claim 6, characterized in that  $M_1$  is an ammonium group selected from tetraalkylammonium, pyridinium, alkylpiperidinium, alkylpiperazinium, alkylpyrrolidinium and tetraalkylanilinium groups.
8. Process according to claim 6, characterized in that  $M_1$  is a phosphonium group selected from arylphosphonium and alkylarylphosphonium groups.
- 10 9. Process according to claim 6, characterized in that the halide of formula (X) is lithium chloride.
- 15 10. Process according to any one of the preceding claims, characterized in that, if n is equal to zero, the compounds of formula (IV) correspond more particularly to general formula (IVa):



20

in which:

- 25  $R_6$  is a hydrogen atom, a linear or branched  $C_{1-8}$  lower alkyl group, preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or pentyl, or a  $C_{1-15}$  arylalkyl group, e.g. benzyl, phenylethyl or methylbenzyl, which can optionally be substituted by a  $C_{1-5}$  alkoxy or alkyl, especially of the methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, methoxy, ethoxy, propoxy, butoxy or pentoxy type;

- 30  $R_7$ ,  $R_8$  and  $R_{11}$ , which are identical or different, independently are a hydrogen atom, a  $C_{1-8}$  lower alkyl group, especially of the methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or pentyl type, a  $C_{6-12}$  aryl group, e.g. phenyl, 1-naphthyl or 2-naphthyl, or a  $C_{7-12}$  arylalkyl group, preferably benzyl, phenylethyl or methylbenzyl, it being possible for said aryl or arylalkyl groups to

be substituted, with the proviso that R<sub>7</sub> and R<sub>8</sub> are different;

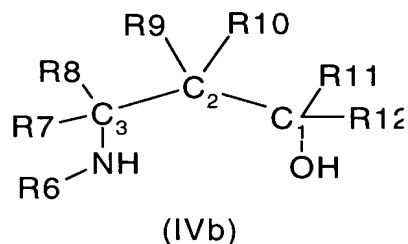
R<sub>6</sub> and R<sub>7</sub> together can form an optionally substituted C<sub>1-6</sub> alkylene group, e.g. methylene, dimethylene, trimethylene or tetramethylene;

R<sub>8</sub> and R<sub>11</sub> together can form an alkylene group that is optionally substituted or fused with a benzene ring, e.g. trimethylene, tetramethylene, pentamethylene, o-phenylenemethylene or o-phenylenedimethylene; and

C<sub>1</sub> and/or C<sub>2</sub> are an asymmetric carbon atom.

11. Process according to claim 10, characterized in that said optically active product of formula (IVa) is (S)- or (R)-β,β-diphenyl-2-pyrrolidinylmethanol.

12. Process according to any one of the preceding claims, characterized in that, if n is equal to 1, the compounds of formula (IV) correspond more particularly to general formula (IVb):



in which:

R<sub>6</sub> is a hydrogen atom, a linear or branched C<sub>1-8</sub> lower alkyl group, especially of the methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or pentyl type, or a C<sub>1-15</sub> arylalkyl group, e.g. benzyl, phenylethyl or methylbenzyl, which can optionally be substituted by a C<sub>1-5</sub> alkoxy or alkyl, especially of the methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, methoxy, ethoxy, propoxy, butoxy or pentoxy type;

R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub> and R<sub>12</sub>, which are identical or different, independently are a hydrogen atom, a C<sub>1-8</sub> lower alkyl group, especially of the methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or pentyl type, a C<sub>6-12</sub> aryl group, especially phenyl, 1-naphthyl or 2-naphthyl, or a C<sub>7-12</sub> arylalkyl group, especially benzyl, phenylethyl or methylbenzyl, it being possible for said aryl or arylalkyl groups to be substituted, with the proviso that R<sub>7</sub> and R<sub>8</sub>

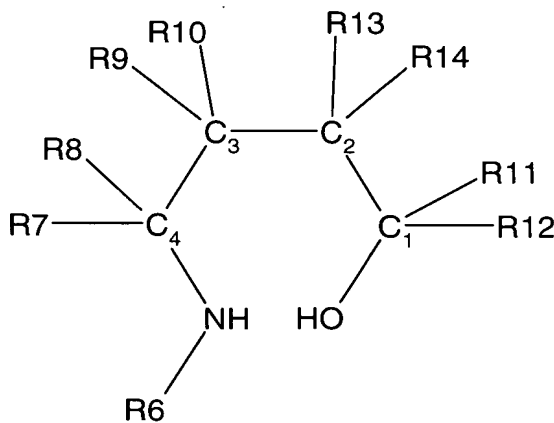
are different;

$R_6$  and  $R_7$  together can form an optionally substituted  $C_{3-6}$  lower alkylene group, especially methylene, dimethylene, trimethylene or tetramethylene;

- 5  $R_8, R_{11}$  or  $R_8, R_9$  or  $R_9, R_{11}$  together can form an alkylene group that is optionally substituted or fused with a benzene ring, especially trimethylene, tetramethylene, pentamethylene, o-phenylenemethylene or o-phenylenedimethylene; and

$C_1$  and/or  $C_2$  and/or  $C_3$  are an asymmetric carbon atom.

- 10 13. Process according to claim 12, characterized in that said optically active product of formula (IVb) is (S)- or (R)- $\beta, \beta$ -diphenyl-2-pyrrolidinyethanol, (S)- or (R)- $\beta, \beta$ -di(t-butyl)-2-piperidinyethanol or (S)- or (R)-2-phenyl-4-hydroxypiperidine.
- 15 14. Process according to any one of the preceding claims, characterized in that, if n is equal to 2, the compounds of formula (V) correspond more particularly to general formula (IVc):



(IVc)

20

in which:

$R_6$  is a hydrogen atom, a linear or branched  $C_{1-8}$  alkyl group, especially a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or pentyl group, or a  $C_{1-15}$  arylalkyl group, especially benzyl, phenylethyl or methylbenzyl,

which can optionally be substituted by a C<sub>1-5</sub> alkoxy or alkyl, especially a methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, methoxy, ethoxy, propoxy, butoxy or pentoxy group;

5 R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub> and R<sub>14</sub>, which are identical or different, independently are a hydrogen atom, a C<sub>1-8</sub> lower alkyl group, especially a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or pentyl group, a C<sub>6-12</sub> aryl group, especially a phenyl, 1-naphthyl or 2-naphthyl group, or a C<sub>7-12</sub> arylalkyl group, e.g. benzyl, phenylethyl or methylbenzyl, it being possible for said aryl or arylalkyl groups to be substituted by a C<sub>1-5</sub> alkyl or a ... such as those  
10 mentioned above, with the proviso that R<sub>7</sub> and R<sub>8</sub> are different;

R<sub>6</sub> and R<sub>7</sub> together can form an optionally substituted C<sub>3-6</sub> lower alkylene group, especially a methylene, dimethylene, trimethylene or tetramethylene group;

R<sub>9</sub> and R<sub>8</sub> together can form an alkylene group that is optionally substituted or fused with a benzene ring, e.g. trimethylene, tetramethylene, pentamethylene,  
15 o-phenylenemethylene or o-phenylenedimethylene; and

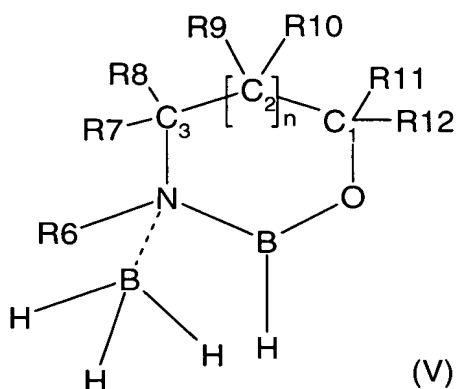
C<sub>1</sub> and/or C<sub>2</sub> and/or C<sub>3</sub> and/or C<sub>4</sub> are an asymmetric carbon atom.

15. Process according to any one of the preceding claims, characterized in that the amount of compound of formula (IV) used in the reaction is between 0.005 and  
20 0.2 equivalent, based on the metal borohydride.

16. Process according to any one of the preceding claims, characterized in that the compound of formula (IV) is optically active  $\alpha,\alpha$ -diphenylpyrrolidin-2-ylmethanol.  
25

17. Process for the synthesis of chiral alcohols, characterized in that it comprises the in situ preparation of the complex according to any one of claims 1 to 16, followed by the introduction of a ketone to be reduced.

30 18. Process according to claim 17, characterized in that said complex is a chiral compound of general formula (V):

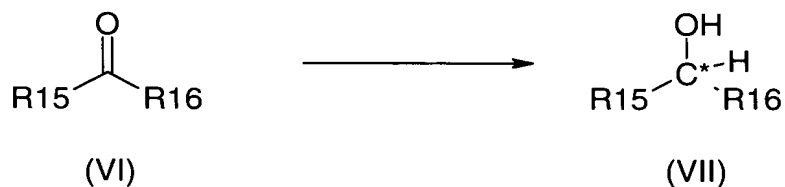


in which:

5      R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub> and n are as defined in formula (IV) and C<sub>1</sub>  
and/or C<sub>2</sub> and/or C<sub>3</sub> are an asymmetric carbon atom.

19.    Process according to claim 17 or 18, characterized in that said ketones  
correspond to general formula (VI) below and are reduced to optically active  
alcohols of general formula (VII) below:

10



15      in which R<sub>15</sub> and R<sub>16</sub> are different, are inert to reduction and are optionally  
substituted organic radicals which together can form a saturated or unsaturated  
ring.

20.    Process according to any one of claims 17 to 19, characterized in that the  
asymmetric reduction of the compounds of formula (VI) takes place under the  
following operating conditions:

20

- the compounds of formula (VI) are added slowly over a period of  
between 0.5 and 10 hours, with stirring;
- the temperature is between 0°C and 75°C; and
- the amount of prochiral ketone is 10 to 1000 times greater than that of the  
amino alcohol of formula (IV) used in the reaction.

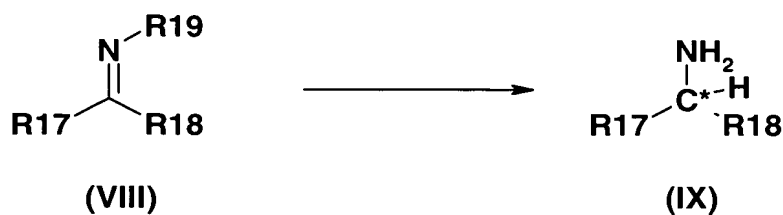


21. Process according to claim 20, characterized in that the compound of formula (VI) is 1-(2-thienyl)-3-chloropropanone and is added in an amount 50 to 100 times greater than that of the optically active compound  $\alpha,\alpha$ -diphenylpyrrolidin-2-ylmethanol.

5

22. Process according to any one of claims 17 to 21, characterized in that the complex of formula (V), prepared in situ, is used to reduce the ether oximes of general formula (VIII) to the corresponding optically active amines of general formula (IX):

10



in which:

15  $\text{R}_{17}$  and  $\text{R}_{18}$  are different and the chirality of the secondary amine obtained is defined by the carbon atom carrying the amine group;

$\text{R}_{17}$  and  $\text{R}_{18}$  are inert to reduction, are organic radicals independently substituted by which group and together can form a saturated or unsaturated ring; and

$\text{R}_{19}$  is an alkoxy, an aryloxy or an arylalkoxy.